C. Remarks

Applicants wish to thank Examiner for granting a telephone interview on December 3, 2003 in which Applicants' further presented their points of novelty in the present invention.

Claims 1-21 and 23-38 are pending in the application. Claims 37 and 38 have been amended. The claim amendments are offered to correct certain formal defects in the claims as filed and are offered free of any intent to narrow the scope of what Applicants' consider as their invention. Support for the amendments may be found throughout the specification as filed, including the documents and references cited and incorporated therein.

The pending claims have all been rejected for obviousness. Applicants respectfully request reconsideration of the claims in light of the following remarks.

Claims 1-21 and 23-38 stand rejected under 35 USC § 103(a) as being unpatentable over Garbe et al. (WO 96/08229) in view of Cleary (EP 0483105 A1). The rejection is respectfully traversed. Reconsideration and withdrawal of this rejection is requested.

The Office Action cites statements made in a prior office action, and reiterates, in part: The Garbe reference teaches a transdermal drug delivery device compromising a backing and a matrix comprising a copolymer, a softener and a drug. The compolymer in the Garby reference comprises one or more A monomers selected from the group consisting of alkyl acrylates containing 4 to 10 carbon atoms in the alkyl group and alkyl methacrylates containing 4 to 10 carbon atoms in the alkyl group; one or more ethylenically unsaturated B monomers copolymerizable with the A monomers and a macromonomer copolymerizable with the A and B monomers. The macromonomer in the Garby reference is generally present in an amount of 0.1 to 30% by weight based on the total weight of all monomers in the copolymer. The Examiner indicates that the Garby reference does not expressly disclose the exact concentration ranges in the instant claims nor does it teach specifically that fentanyl in the drug delivered. The Cleary reference teaches a transdermal delivery device comprising fentanyl and absorption enhancers in a matrix which are fatty acid esters or fatty alcohol ethers.

In order to establish a *prima facie* case of obviousness, the Patent Office must demonstrate that (1) there is a suggestion or motivation in the prior art to modify or combine reference teachings, (2) one skilled in the art would have had a reasonable expectation of success in making the modification or combination, and (3) the prior art reference(s) disclose all of the claim limitations. The fact that one of ordinary skill in the art would have had the capability to modify the method disclosed in the prior art reference(s) is not sufficient. MPEP 2143.01. The prior art reference(s) must provide a motivation or reason for making the changes. MPEP 2142; *Ex parte Chicago Rawhide Manufacturing Co.*, 226 USPQ 438 (PTO Bd. App. 1984). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure.

As stated in the Examiner interview, given the well-known difficulties associated with solubilizing fentanyl, even if one had been motivated to use a higher concentration of the drug, there would have been no expectation of success or reason to make a change by incorporating fentanyl into the Garbe device in the amounts recited in the present claims while still providing a composition that was substantially free of undissolved drug. The Garbe reference teaches that the drug is preferably fully dissolved, but the Garbe reference fails to suggest that fentanyl in particular could be successfully formulated in an acylate composition in amounts between about 8% and about 30% without the presence of a substantial amount of undissolved fentanyl. The Garbe reference fails to demonstrate that fentanyl could be dissolved in large amounts, e.g., greater than 8 percent by weight, wherein the matrix would remain substantially free of undissolved drug. Additionally, the Cleary does not cure the defects of the Garbe reference. The Cleary reference fails to demonstrate any ability to dissolve fentanyl at high concentrations in transdermal devices.

Further, the Garbe reference states that in a preferred embodiment the drug is substantially fully dissolved. There is no necessity, however, that the devices of Garbe are limited to instances where the drug is fully dissolved. In fact, there is no indication in Garbe that any substantial number of the drugs recited could indeed be formulated over the entire range described as typical (0.01 to 30 percent) in the preferred embodiment where the drug is fully dissolved.

Applicants direct Examiner to Examples 7-15 in Specification on page 24 as proof of the criticality of the range data. Examples 7 to 15 showing fentanyl dissolved in transdermal devices at concentrations ranging from 11.6 to about 23 percent fentanyl. These high concentrations of dissolved drug allow for a remarkably sustained duration of delivery from devices of the present invention. Additionally, Applicant's direct Examiner to Table 4 (Human Cadaver Skin Permeation, Average Cumulative Amount Penetrated). Table 4 demonstrates that delivery is maintained or in some cases increases over the time period from 48 to 120 hours. It would typically be expected that having reached an initial maximum delivery rate across the skin (which usually takes 24 to 30 hours for fentanyl), the amount penetrated over a given time period (i.e, flux) will then decrease as the device becomes depleted of drug and the thermodynamic driving force is reduced. As shown, the average flux rates tend to increase over the time period from 1 to 5 days, which is an surprising result and an important benefit compared to prior art devices that show decreasing flux rates after 24 to 48 hours.

In view of the arguments and amendments offered herein, Applicants respectfully submit that the Examiner's grounds for objection and rejection are overcome and respectfully solicit reconsideration and withdrawal of the rejections and allowance of the application.

Respectfully submitted,

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